Effect of endothelial responses on sepsis-associated organ dysfunction

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Abstract

Sepsis-related organ dysfunction is associated with increased morbidity and mortality. Previous studies have found that the endothelium plays crucial roles in maintaining the vascular permeability during sepsis, as well as in regulating inflammation and thrombosis. During sepsis, endothelial cells may release cytokines, chemokines, and pro-coagulant factors, as well as express adhesion molecules. In general, endothelial responses during sepsis typically inhibit bacterial transmission and coordinate leukocyte recruitment to promote bacterial clearance. However, excessive or prolonged endothelial activation can lead to impaired microcirculation, tissue hypoperfusion, and organ dysfunction. Given the structural and functional heterogeneity of endothelial cells in different organs, there are potential differences in endothelial responses by organ type, and the risk of organ damage may vary accordingly. This article reviews the endothelial response observed in sepsis and its effects on organ function, summarizes current progress in the development of therapeutic interventions targeting the endothelial response, and discusses future research directions to serve as a reference for researchers in the field.

Keywords: Endothelial response; Sepsis; Organ dysfunction; Vascular permeability; Microcirculation

Introduction

Sepsis, defined as organ dysfunction caused by a dysregulated host response to infection, is associated with elevated morbidity and mortality.[1] Studies have shown that the endothelium plays crucial roles in terms of maintaining vascular permeability, as well as regulating inflammation and blood coagulation, during sepsis.[2–4] When activated by sepsis, endothelial cells (ECs) release cytokines, chemokines, and pro-coagulation factors and increase their expression of adhesion molecules. Glycocalyx damage and vascular dysfunction may compromise microcirculation in endothelial tissues, which can cause organ damage or even death if left untreated.[5] In general, endothelial responses during sepsis typically restrain bacterial dissemination and coordinate leukocyte recruitment to promote bacterial clearance. However, excessive or prolonged endothelial activation can lead to compromised microcirculation, tissue hypoperfusion, and organ dysfunction. Given the potential variations in endothelial responses among different organs, the risk of organ injury may differ accordingly as well. Therefore, investigating the pathways underlying sepsis-induced endothelial activation may offer a promising approach for mitigating sepsis-induced organ dysfunction. This review aims to summarize the various endothelial responses that have been observed during sepsis and their respective impacts on organ function, as well as outline advancements and future research directions in therapeutic interventions for sepsis that target endothelial responses.

Endothelial Responses in Sepsis

Glycocalyx degradation

The glycocalyx, a polysaccharide–protein complex layer on vascular EC surfaces, plays a vital role in maintaining vascular homeostasis by regulating permeability and leukocyte adhesion and preventing microvascular thrombosis.[6,7] During sepsis, glycocalyx degradation is linked to several pathophysiological changes.[8–11] First, it decreases vascular barrier function, leading to increased permeability and interstitial edema. It also contributes to reduced functional capillary density and increased erythrocyte volume, which are indicative of the abnormal distribution of microcirculation blood flow seen in sepsis. This degradation compromises endothelial protection, allowing inflammatory factors to directly affect ECs, activate adhesion factors, and initiate inflammation-mediated

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000003342

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Chinese Medical Journal 2024;XX(XX)

Received: 30-03-2024; **Online:** 06-11-2024 **Edited by:** Sihan Zhou and Xiuyuan Hao

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endothelial injury. Moreover, the degradation of glycocalyx subjects endothelial surfaces to shear forces from blood flow. This results in mechanical injury, platelet adhesion, and microthrombosis–all of which further disrupt microcirculation and tissue perfusion.[12] It also mediates interactions between white blood cells and ECs, hindering the clearance of inflammation and promoting inflammatory cytokine storms. Notably, glycocalyx recovery after acute injury takes approximately 5–7 days, potentially explaining the persistent microcirculatory dysfunction often seen in septic shock despite hemodynamic resuscitation and optimization.[5]

EC death

During sepsis, ECs are vulnerable to various types of cell death–including apoptosis, necrosis, necroptosis, and pyroptosis[13]—all of which contribute to endothelial dysfunction and impact vascular integrity and organ function. Apoptosis, characterized by caspase activation and DNA fragmentation, is a programmed cell death process that occurs in ECs in response to cellular stress.[14] Necrosis, an unprogrammed form of cell death, is also prevalent in septic ECs. It is typically caused by severe cellular injury or changes in organ perfusion and blood volume associated with the condition. Necrotic apoptosis, a programmed variant involving receptor-interacting protein 1 (RIP1) and RIP3 kinases that is activated by toxic factors from pathogens or the host response, may also occur.[15] Pyroptosis, another mode of cell death often observed during sepsis, involves inflammasome activation. This results in caspase-1 activation, cell membrane rupture, and the release of inflammatory mediators that further exacerbate inflammation and endothelial damage.[16] Mitochondrial dysfunction in ECs during sepsis reduces adenosine triphosphate (ATP) production and increases reactive oxygen species (ROS) generation, promoting apoptosis and further compromising endothelial viability.[17] In response to sepsis-induced stress, ECs transition to proinflammatory, proadhesive, and procoagulative states, all of which exacerbate endothelial damage and cell death.[18] Collectively, these mechanisms compromise vascular integrity, leading to microcirculatory dysfunction and eventual organ failure.

Tight junction (TJ) destruction

During sepsis, inflammatory mediators such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) directly damage ECs, resulting in decreased expression of TJ proteins such as claudin-5, occludin, and zonula occludens protein 1 (ZO-1), thereby disrupting blood vessel barrier function.[19,20] Enhanced oxidative stress in sepsis leads to the overproduction of ROS and reactive nitrogen species (RNS), further damaging ECs and compromising TJ integrity. Additionally, the upregulation of the vascular endothelial growth factor (VEGF) during sepsis contributes to the breakdown of TJs between ECs.[21] Activated platelets release various mediators that disrupt TJs and promote inflammation and thrombosis when they interact with ECs. Furthermore, sepsis-induced EC apoptosis and damage to intercellular connections can lead to alterations in endothelial permeability and plasma extravasation. Collectively, these mechanisms culminate in the breakdown of connections between ECs during sepsis, exacerbating vascular dysfunction and contributing to the pathogenesis of the condition.

Immune response disorder

During sepsis, ECs become activated via various pathways such as Nuclear Factor kappa B (NF-κB) and mitogen-activated protein kinases, releasing inflammatory factors that activate immune cells and initiate an inflammatory response.[22] Although several animal studies have reported the effectiveness of endothelium-related anti-inflammatory strategies for treating sepsis,[23,24] caution must be exercised when interpreting these results, owing to the complex pathophysiology of sepsis in humans. ECs regulate leukocyte adhesion and migration by expressing surface adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which facilitate immune cell localization and aggregation at infection sites. Plasma levels of adhesion molecules such as E-selectin, VCAM-1, and ICAM-1 are significantly elevated in patients with sepsis, correlating with the severity of organ failure.[22] Blocking adhesion molecules is considered a potential treatment for sepsis[25]; however, complete suppression of leukocyte aggregation can be harmful, as it is needed to kill microorganisms and limit the transmission of sepsis.

Impaired anticoagulation and fibrinolytic function

The inflammatory mediators and cytokines released as a result of EC activation during sepsis can affect anticoagulation and fibrinolytic systems, both directly and indirectly. For instance, TNF-α and IL-1 can promote tissue factor (TF) expression by blood vessel ECs, promoting thrombosis. TF is a procoagulant factor that enhances the coagulation cascade and thrombosis.[26,27] Additionally, EC damage inhibits the activities of anticoagulant proteins C and S, suppresses the anticoagulant system, and promotes thrombosis.[28] EC injury may also suppress the fibrinolytic system, slowing thrombus dissolution by increasing the release of plasminogen inhibitors such as plasminogen activator inhibitor-1 (PAI-1).[29,30] Elevated plasma PAI-1 levels in patients with sepsis are associated with increased mortality and multiple organ failure.[31] The inflammatory mediators and adhesion molecules released during EC activation promote platelet activation and aggregation during sepsis, leading to thrombus formation, obstruction of microvascular blood flow, and aggravation of tissue ischemia and hypoxia. Platelet–leukocyte aggregates deplete platelets during sepsis, releasing neutrophil extracellular traps (NETs) that limit bacterial transmission and attach to the endothelium, further exacerbating local inflammation and reducing tissue perfusion.[32]

Impaired vascular tone

During sepsis, damaged ECs may increase their release of vasoconstrictors.[33] Endothelin, a potent vasoconstrictor,

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acts directly on vascular smooth muscle cells, causing vasoconstriction and increasing vascular resistance. Conversely, ECs may also reduce their release of vasodilators such as nitric oxide (NO).[34] NO, a key vasodilator, induces vasodilation and decreases vascular tone by relaxing vascular smooth muscle cells. Impaired EC function and various effects mediated by inflammation may reduce NO synthesis and impair vasodilation. Additionally, EC injury or activation during sepsis can cause vascular leakage that induces tissue edema and affects local vascular tone. Moreover, ECs damaged by sepsis may increase their release of prothrombotic factors. This can lead to thrombosis, microcirculatory disturbances, and subsequent vascular tone alterations [Figure 1].

Impaired endothelium-dependent relaxation in sepsis refers to a reduced level of response to stimuli that typically induce vasodilation in ECs, thus hindering the process. Endotoxin exposure impairs endothelium-dependent relaxation through multiple mechanisms—including the obstruction of the NO synthesis pathway, impaired EC function, influencing inflammatory mediators, and increased oxidative stress.[35–37] Dysfunction of these mechanisms decreases EC responses to vasodilatory stimuli, thereby affecting vascular function.

Organ specificity of the endothelial response

There are differences in the structure, function, and receptors expressed by ECs in different organs that determine their heterogeneity [Table 1].[38,39] In terms of TJs, ECs in the brain are more highly expressed because they are required to maintain the integrity of the blood-brain barrier (BBB) and blood filtration barrier. TJs are less expressed in post-capillary venules because they are needed to guarantee optimal exchange between blood and tissue. ECs in the lungs may have more microvilli structures to increase the surface area for gas exchange and facilitate vasodilation or contraction during gas exchange. During sepsis, the lung endothelium expresses more adhesion molecules and has a higher permeability than the kidneys and liver.[40,41] Differences in phenotypes and outcomes of sepsis associated with pneumonia, meningitis, and nephritis may be related to the organ specificities of different ECs.

ECs play important roles in immune regulation by mediating inflammatory responses, leukocyte adhesion and migration, and antigen presentation. They exhibit different immunomodulatory capacities in different tissues and organs, because they express different types and amounts of immunomodulatory molecules, receptors, and signaling pathways in order to help them adapt to varying immune

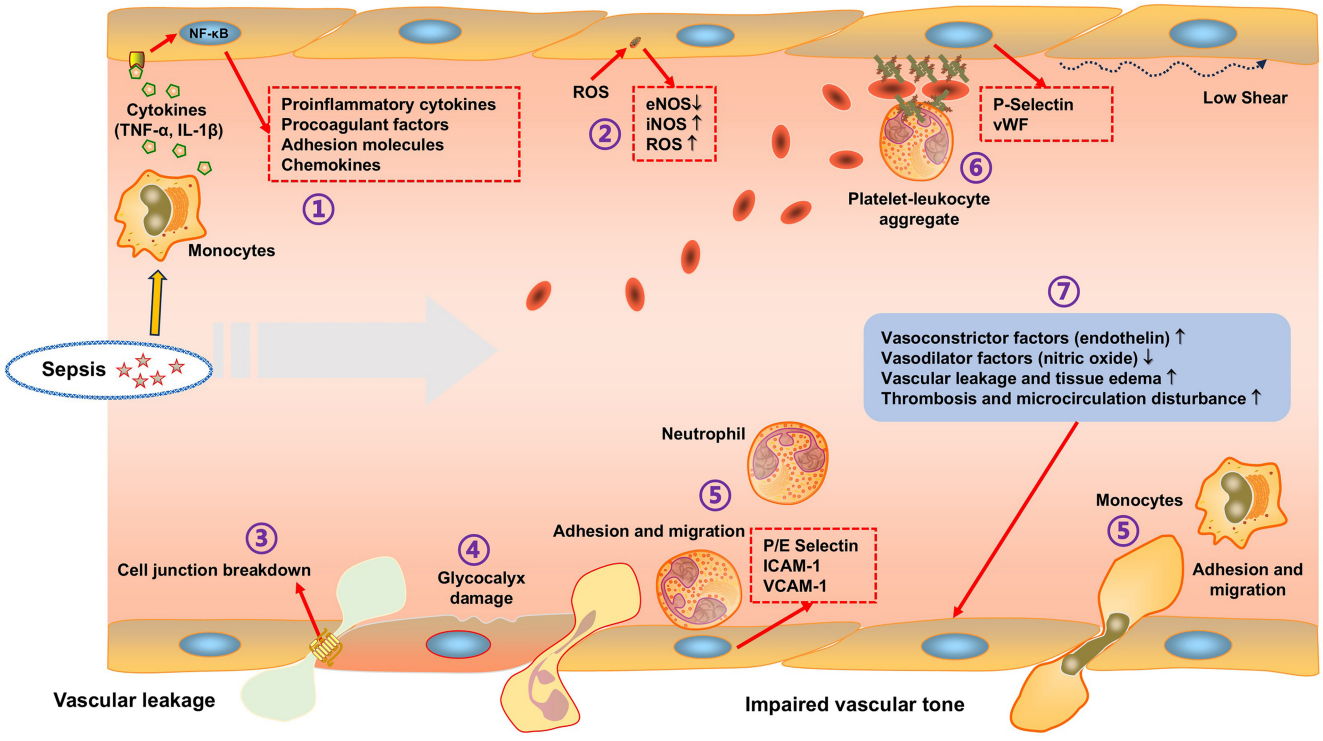

Figure 1: Endothelial responses to sepsis. ① During sepsis, various inflammatory factors activate ECs, leading to the activation of intracellular signal transduction. This activates transcription factors, increasing the transcription of pro-inflammatory cytokines, chemokines, adhesion molecules, and pro-coagulant factors. ② During sepsis, oxidative stress leads to dysregulation of NO synthase activity, resulting in excessive production of NO. Concurrently, sepsis induces ECs to produce ROS, which further damage them. ③ Sepsis causes disruption of intercellular connections between ECs, leading to increased endothelial permeability. ④ During sepsis, endothelial glycocalyx damage leads to increased inflammation, thrombosis, and hyperosmolarity. ⑤ Sepsis triggers EC activation, leading to increased surface expression of E-selectin, P-selectin, VCAM-1, and ICAM-1; followed by leukocyte rolling, adhesion, and migration on ECs. ⑥ Activated ECs express surface molecules such as vWF and P-selectin, mediating the formation of platelet–leukocyte aggregates and thereby promoting thrombus formation. ⑦ Damaged ECs can increase their release of vasoconstrictor factors and decrease their release of vasodilator factors. Vascular leakage and tissue edema can affect the local vascular tone. In addition, thrombosis and microcirculatory disturbances both alter vascular tone. NF-κB : Nuclear factor kappa B; ECs: Endothelial cells; eNOS: Endothelial nitric oxide synthase; E-Selectin: Endothelial selectin; ICAM-1: Intercellular adhesion molecule-1; IL-1: Interleukin-1; iNOS: Inducible nitric oxide synthase; NO: Nitric oxide; P-Selectin: Platelet selectin; ROS: Reactive oxygen species; TNF-α: Tumor necrosis factor-α; VCAM-1: Vascular cell adhesion molecule-1; vWF: von Willebrand factor.

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Table 1: Organ heterogeneity of ECs.

Organ	Characteristic	Heterogeneity
Heart	TJ	Has abundant cell connections and can effectively block macromolecular substances and particles from entering cells.
	Cellular metabolism	More efficient metabolism that relies heavily on the glycolytic pathway for energy, rather than oxidative phosphorylation.
	Angiogenic potential	High angiogenic potential that can provide sufficient oxygen and energy for normal growth and maintenance of function in the heart.
	Response to hemodynamics	Can sense changes in blood flow and shear force, then regulate vascular structure and function through signal transduction mechanisms.
	EndMT	Can transform into mesenchymal cells via endothelium–mesenchymal transdifferentiation and participate in both myocardial fibrosis and cardiac remodeling.
Brain	TJ	Tight intercellular junctions not only ensure the integrity of the BBB, but also create high transendothelial impedance, limiting the diffusion of substances through paracellular pathways.
	Transport system	A series of specific transporters are expressed that selectively transport essential nutrients from the blood to the brain parenchyma while excluding potentially harmful substances.
	Cytoplasmic reticulum	Brain ECs typically lack cytoplasmic reticula, unlike other ECs. This reduces the transport of substances, through cellular endocytosis.
	Metabolic enzymes	Contain certain particular metabolic enzymes that play significant roles in drug metabolism and detoxification.
	Immune privileged environment	Participates in shaping the immune privileged environment of the CNS, limiting the entry of immune cells and protecting it from exogenous pathogens.
Lung	Gas exchange	Not only is it very thin, but it also covers a very large surface area and is arranged around the alveoli to form an alveolar capillary membrane that is conducive to the rapid diffusion of gases.
	Inflammation	Can express a variety of adhesion molecules and promote immune cell recruitment.
	Vascular permeability	Regulation of vascular permeability through the expression of TJ and AJ proteins is critical for edema formation and alveolar fluid balance.
	Thrombosis	Typically express anticoagulant factors such as tPAI and anticoagulant protein C, as well as fibrinolytic factors such as tPA.
	Response to hypoxia	Able to sense and respond to hypoxic conditions, as well as participate in hypoxia-induced angiogenesis by producing specific cytokines and vasoactive substances.
Liver	High permeability	The lack of typical intercellular TJs makes the sinusoidal spaces of the liver highly permeable, which is conducive to the exchange of substances between liver cells and the blood.
	Filter features	Can act as a "filter" to regulate metabolite transport from the intestine to hepatocytes and control the immune response to viral infection independently of leukocyte extravasation.
	Liver regeneration	Liver regeneration is maintained through Tie1 signaling-dependent production of Wnt.
	Angiopoietin receptor expression	Expresses angiopoietin receptors Tie1 and Tie2. These receptors have a regulatory role in liver partitions, and their activation is related to the regulation of Wnt expression in liver vessels.
	Anticoagulation function	Capable of synthesizing and releasing a variety of coagulation and anticoagulation factors.
Kidney	Filtration and absorption	Specialized filtration membranes are formed in the glomerulus, which is a key part of the process of blood filtration and urine formation. The capillary network surrounding the renal tubules is highly permeable, facilitating the exchange of waste and nutrients.
	Charge selective barrier	The ECs of the glomerulus are negatively charged, helping to prevent negatively charged plasma proteins such as albumin from passing through the filtration membrane.
	Vasoreactivity	Responds to vasoactive substances such as angiotensin II and NO and participates in regulating the vascular tone and blood pressure of the kidneys.
	Synthesis and secretion	Can synthesize and release a variety of bioactive molecules, including VEGF and ET-1. These molecules are involved in angiogenesis and the functional regulation of the kidneys.
	Anticoagulation	Antithrombin and other anticoagulant molecules can be expressed to help prevent blood from clotting in the kidneys.

AJ: Adherens junction; BBB: Blood-brain barrier; CNS: Central nervous system; ECs: Endothelial cells; EndMT: Endothelial-to-mesenchymal transition; ET-1: Endothelin-1; NO: Nitric oxide; TJ: Tight junction; VEGF: Vascular endothelial growth factor.

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environments and functional needs. Recent single-cell studies have revealed significant tissue-specific differences in the expression patterns of EC costimulatory molecules, chemokines, and cytokines.[42,43]

Endothelial Response of Various Organs During Sepsis

Endothelial response in lung injury

Sepsis-induced lung injury is a serious pathological condition that is typically associated with systemic infections and inflammatory responses.[25,44,45] Sepsis-induced lung injury is a form of acute respiratory distress syndrome (ARDS) that has an in-hospital mortality rate of >40%. Sepsis-induced acute lung injury (ALI) represents a serious threat to human health. ECs—particularly those of pulmonary capillaries—are the first line of defense against sepsis in the lungs. Sepsis can lead to acute injury of ECs in the pulmonary capillaries, which in turn causes pulmonary edema and hypoxemia. Endothelial injury and vasoconstriction lead to an increase in pulmonary vascular resistance, which increases the load on the right side of the heart. This may lead to right ventricular overload, right heart insufficiency, and eventually heart failure. EC dysfunction, one of the key features of ALI, is associated with the loss of vascular endothelial barrier integrity. This leads to increased vascular permeability, which allows for the leakage of plasma components into the alveoli and the formation of pulmonary edema. These pathological changes lead to fluid accumulation in the alveolar air space, which in turn triggers respiratory failure.[46] EC activation can lead to the release of coagulation factors, increasing the risk of thrombosis and further impairing blood flow to the lungs and other organs. ECs amplify the inflammatory response and exacerbate tissue damage by expressing pattern recognition receptors (PRRs) and releasing damage-associated molecular patterns (DAMPs) such as extracellular nicotinamide phosphoribosyltransferase (eNAMPT).[47] One study revealed the heterogeneity of pulmonary capillary ECs in sepsis using single-cell RNA sequencing (scRNA-seq), which classified them into three subpopulations: Capillary-1, Capillary-2, and Capillary-3. $CD74^+$ Capillary-3 cells are crucial for immune reactions during sepsis, particularly with regard to antigen processing and presentation. Platelet reactive protein-positive capillary cell 1 ($Plat^+$ Capillary-1) cells are crucial for attachment to neutrophils during sepsis and participate in the innate immune reaction via ICAM-1-mediated adhesion. This suggests that ECs are involved not only in the immune response but also in inflammatory and coagulation processes in sepsis-induced ALI. Although ECs are typically not considered immune cells, they show immunomodulatory functions in sepsis—including antigen presentation through major histocompatibility complex (MHC) molecules, intercellular communication, and other immunomodulatory functions.[48] Studies have shown that unfractionated heparin preconditioning protects against LPS-induced pulmonary endothelial barrier dysfunction and is associated with VE-cadherin stabilization and PI3K/Akt/NF-κB signaling.[49] Another study revealed that a specific reduction in the Poldip2 EC type had a protective effect against LPS-induced ALI, emphasizing its crucial role in barrier function.[50]

Endothelial reaction during kidney injury

Sepsis-induced kidney injury, also known as sepsis-associated kidney injury, is a common clinical complication. Acute kidney injury (AKI) occurs in about 50% of patients with sepsis and is associated with increased morbidity and mortality.[51] It occurs as a result of an inflammatory response and circulatory disorders caused by systemic infections. Sepsis-associated AKI is extremely life-threatening because it not only increases morbidity and mortality in patients but may also lead to long-term renal dysfunction and even the need for long-term dialysis treatment.[52] A number of studies have highlighted the significant impact of EC damage and malfunction on the development of septic AKI. EC injury may lead to vasoconstriction, increased vascular permeability, and thrombosis—all of which can affect the renal blood flow and oxygen supply, consequently leading to kidney injury.[41,53] Angiotensin-converting enzyme (ACE) is an EC surface enzyme that holds a crucial position within the renin–angiotensin–aldosterone system (RAAS). During septic shock, damage to ECs can result in ACE malfunction, subsequently affecting the standard control of the RAAS and intensifying vasodilatory shock and AKI.[54] Research has revealed links between the depletion of soluble vascular endothelial cadherin (sVE-cadherin), the onset of AKI, and heightened organ dysfunction in patients with sepsis. This element is crucial for adhesion junctions between ECs. It also significantly influences the regulation of vascular integrity, endothelial permeability, and angiogenesis.[55] The influx of calcium ions (Ca^{2+}) in ECs and the subsequent increase in intracellular calcium concentration ($[Ca^{2+}]i$) are crucial steps during the establishment of endothelial hyperpermeability. Studies have shown that endotoxins upregulate the expression of transient receptor potential melastatin 7 (TRPM7) via the TLR4/NOX-2/ROS/NF-κB pathway, inducing a TRPM7-dependent EC calcium overload. The inhibition of TRPM7 expression can suppress renal vascular hyperpermeability and prevent renal dysfunction.[56] Additionally, following LPS stimulation or cecal ligation and puncture (CLP), transient receptor vanilloid subtype 4 (TRPV4) expression increases in mouse glomerular ECs (MGECs), leading to elevated intracellular calcium levels. Inhibiting TRPV4 expression can decrease the phosphorylation and translocation of the inflammatory transcription factors NF-κB and IRF-3 in MGECs, thereby alleviating endothelial inflammation and improving survival rates.[57]

Endothelial response during brain injury

Sepsis-associated encephalopathy (SAE) is a widespread condition that occurs without direct central nervous system infection. Its clinical symptoms include cognitive impairment, disturbance of consciousness, and psychological disorders. It is a common organ dysfunction associated with sepsis, with an incidence of up to 70% in intensive care units, and its severity is correlated with mortality.[58,59] The main pathogenesis of SAE includes

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BBB damage, dysregulation of inflammatory responses, neuroinflammation, oxidative stress, and changes to cerebral microcirculation.[60,61] The BBB prevents pathogens and other harmful substances from entering the central nervous system. Therefore, BBB damage is a key factor in the development of SAE. ECs are crucial components of the BBB that play a vital role in maintaining its stability and regulating its permeability.[62] During sepsis, the TJ proteins between ECs are disrupted, altering the structure and function of the BBB and resulting in cerebral vascular damage or impaired brain function.[63,64]

ECs and immune cells work together to maintain BBB integrity.[62] TNF-α, released during sepsis, induces necrotic apoptosis of ECs, altered vascular permeability, increased microglia activation, monocyte infiltration into the brain, and increased susceptibility to diseases such as epilepsy.[65] Mast cells interact with brain microvascular ECs (BMVECs) through the histamine/histamine 1 receptor (H1R), while H1R amplifies lps-induced inflammatory responses in BMVEC and affects cognitive function by regulating the TLR2/4-MAPK signaling pathway.[66] However, research has indicated brain ECs respond earlier than microglial cells during sepsis and that most activated microglial cells are located near ECs—implying that the activation of microglial cells may be related to endothelial function. ECs act as sensors of primary peripheral inflammation that initiate a series of acute neuroinflammatory responses.[67,68] Research has shown that soluble epoxide hydrolase (sEH) affects chronic cognitive function, contributing to long-term neurological and psychiatric disorders. In a murine model of sepsis, it was discovered that the prolonged reactivity of sEH in brain ECs, rather than in neuroglial cells, was linked to the persistent cognitive impairments caused by the condition.[68] This further emphasizes the critical role of endothelial damage in sepsis-induced brain injury.

Moreover, in patients with cerebrovascular disorders such as Alzheimer's disease, vascular dementia, and stroke, cerebral perfusion defects and BBB leakage can intensify the effects of sepsis, leading to a rapid decline in cognitive function.[69,70]

Endothelial response in cardiovascular injury

Patients with sepsis often experience cardiac dysfunction, referred to as sepsis-induced cardiomyopathy (SIC), with an incidence rate of up to 70%.[71] Cardiac dysfunction represents one of the major factors affecting the prognoses of patients with sepsis, leading to reduced blood flow to various organs throughout the body and consequently resulting in dysfunction in other organs as well.[71] Currently, there are three main hypotheses regarding the pathogenesis of SIC: (1) cytotoxicity induced by a large number of inflammatory mediators; (2) systemic coagulation activation that leads to microvascular thrombosis and subsequently causing myocardial ischemia; and (3) endothelial dysfunction that results in insufficient tissue perfusion.[72] These pathogenic mechanisms are thought to interact with one another.

Platelets play an important role in thromboinflammatory diseases and their complications. While the undamaged endothelium typically does not interact with them, it undergoes excessive activation and dysfunction during sepsis, promoting platelet adhesion to the inflamed endothelium that confers a more aggressive phenotype. Endothelial injury and platelet activation then promote leukocyte recruitment. The clustering of platelets, neutrophils, and monocytes within vessels leads to microvascular occlusion and the initiation and persistence of systemic inflammatory responses—resulting in the overproduction of pro-inflammatory cytokines and severe oxidative stress.[73] Therefore, inhibiting the adhesion of inflammatory cells to ECs represents an effective method for reducing cardiac injury. For example, Mac-1, a significant member of the β2 integrin family that has high expression levels on monocytes and neutrophils, participates in leukocyte adhesion to endothelia and in processes such as endothelial migration, phagocytosis, and immune system activation. Studies have shown that blocking the activation of Mac-1 can reduce the symptoms of myocardial inflammation.[37] Heat shock protein A12B (HSPA12B) is predominantly expressed in ECs and has been reported to mitigate cardiac dysfunction induced by both sepsis and myocardial infarction. Studies have indicated that HSPA12B prevents severe sepsis-induced cardiomyopathy by modulating the expression of miR-126, a microRNA that targets adhesion molecules and thereby reduces the accumulation of immune cells in the myocardium.[74] Enhancing endothelial barrier function can also mitigate vascular permeability and organ damage in cases of sepsis. Ascorbic acid regulates cytokine production and enhances endothelial barrier function. Research has shown that administering a combination of ascorbic acid and melatonin can alleviate the cardiac and renal damage induced by sepsis.[75] DNA-PKcs are also involved in sepsis-induced cardiac dysfunction. Its activation disrupts mitochondrial homeostasis in ECs, leading to the mtDNA fragmentation of MOTS-c, impairing MOTS-c transcription, causing F-actin depolymerization and endothelial layer degradation, and exacerbating sepsis-induced myocardial microvascular damage. Therefore, inhibiting the activation of DNA-PKcs and enhancing the expression of MOTS-c may represent a therapeutic approach for protecting the endothelial barrier from the effects of sepsis.[76]

Endothelial response during liver injury

Sepsis often causes liver damage. The liver performs essential functions related to immune balance and metabolism, thus representing a significant pathogenic factor during sepsis.[77] Liver dysfunction in patients with sepsis is an early sign of poor prognosis, and acute liver injury is considered a significant factor related to mortality in patients with sepsis.[78]

Liver cells include ECs, immune cells, and hepatic stellate cells.[79] ECs represent the liver's primary line of defense against inflammation and immune responses.[80] Using scRNA-seq, researchers have discovered a significant decrease in the proportion of hepatic ECs in mice with sepsis.[81] Among the remaining ECs, they found an upregulation of genes associated with endothelial dysfunction (e.g., *SERPINE1*, *SELE*, and *FGF23*), inflammation (e.g., *NLRP3*, *NOD2*, and *UBE2N*), apoptosis (e.g., *APAF1*,

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BCL2L11, and *TRP53*), and adhesion molecules (e.g., *VCAM-1* and *SELPLG*). Conversely, the expression of genes related to endothelial junctions (e.g., *TJP1* and *CLDN5*) decreased.[79] The changes in expression levels of these genes in ECs result in an increase in the number of fenestrations around the portal vein, thereby enhancing the permeability of these ECs and promoting immune cell infiltration.[82] This further indicates that EC dysfunction accelerates the development of the acute liver dysfunction induced by sepsis.

Endothelial responses related to coagulation disorders

Patients with sepsis often experience changes in their blood systems, with the majority exhibiting coagulation disorders. Disseminated intravascular coagulation (DIC) represents a frequent and fatal complication of sepsis. Under normal conditions, the endothelium promotes vascular health by expressing molecules that inhibit thrombosis and inflammation.[5] However, following the acute inflammatory response induced by sepsis, ECs lose their antithrombotic properties because of factors such as decreased generation of NO/prostacyclin and glycocalyx degradation. Damaged ECs also release prothrombotic molecules such as von Willebrand factor (vWF) and adhesive molecules, which stimulate platelet adhesion and aggregation.[83] Activated platelets can further exacerbate endothelial damage.[73] These events promote extensive microthrombus formation during sepsis, leading to organ dysfunction. ECs serve as the primary targets of sepsis-related DIC damage caused by activated neutrophils and the release of NETs, ROS, and other pro-inflammatory mediators.[84] The activity of TRPM7 ion channels and α-kinase function are essential for DIC-induced organ dysfunction. Studies have shown that TRPM7 regulates the adhesion of platelets and neutrophils to ECs induced by endotoxins, through its α-kinase function and ion channel activity. TRPM7 mediates the upregulation of adhesion molecules, vWF, and TRPM7 expression—all of which are associated with higher DIC scores and shorter survival times.[85] EC surfaces express an adhesion molecule called PECAM-1. When patients with sepsis develop DIC, the levels of soluble PECAM-1 in the plasma increase significantly. PECAM-1 facilitates interactions between leukocytes and the endothelium. Thus, inhibiting PECAM-1 can accelerate the recovery of the endothelial barrier and play a protective role in terms of preventing septic DIC.[86]

Therapeutic Interventions Targeting Endothelial Responses

During sepsis, endotoxins and inflammatory factors stimulate ECs to undergo a phenotypic shift toward pro-inflammatory, pro-adhesive, pro-coagulant, and apoptotic states.[87] Adequate endothelial alterations play pivotal roles in constraining bacterial dissemination, orchestrating leukocyte infiltration, and facilitating bacterial eradication. Conversely, persistent and exaggerated endothelial phenotypic alterations may culminate in compromised microcirculatory hemodynamics, suboptimal tissue perfusion, and critical organ dysfunction. Therefore, considering the important role of EC dysfunction in the pathogenesis of sepsis, treatments that repair or limit this damage may improve patient outcomes.

In an *in vitro* experiment, methylthiouracil (an anti-thyroid medication) inhibited the release of HMGB1 from human ECs and reduced the levels of TNF-α and IL-6 produced by ECs in a dose-dependent manner. This drug can also inhibit the formation of the endothelial space induced by HMGB1, reduce inflammation, reduce capillary leakage, and improve the survival rate of septic mice. In addition, methylthiouracil inhibits the expression of EC surface adhesion molecules—including ICAM-1, VCAM-1, and E-selectin. It can protect against sepsis-related lung injury.[88] Related research has also confirmed that inhibiting the expression of these adhesion molecules can lead to the reduced migration of inflammatory cells and the decreased tissue levels of inflammatory cytokines,[89] thereby reducing the incidence of and mortality rate associated with sepsis in mice. Furthermore, these adhesion molecules can also be used for the precise delivery of antimicrobial drugs. Antimicrobial drugs can be delivered using nano-metallo-organic frameworks, which are then encapsulated in red blood cell membranes. By modifying the surfaces of red blood cell membrane vesicles with the γ3 peptide, which targets the ICAM-1 proteins on the surfaces of ECs, this approach can be used to reverse sepsis-induced endothelial damage and protect organ function.[90] As red blood cells possess immune tolerance, this approach effectively avoids the clearance of nanomaterials carrying antimicrobial drugs by the immune system, thereby enhancing their bioavailability. However, the development of drugs to reduce vascular leakage and protect EC function has also been met with concerns that this may impair the immune response and affect pathogen clearance. Leakage and cell transport are different processes, and a number of drugs are currently available that inhibit vascular leakage and edema through different mechanisms without compromising innate immunity. For example, antibodies to β1 integrin reduced vascular leakage by reducing EC contraction in septic mice, but had no effect on serum cytokine levels or alveolar neutrophil recruitment.[91] In an extracellular LPS-induced DIC model, miR-19a-3p downregulated the expression of TFs in human umbilical vein ECs and inhibited their procoagulant activity. This treatment also significantly improved the coagulation function indexes, as well as lung and kidney histopathology in DIC rat models. LPS-induced EC apoptosis can lead to organ dysfunction. Studies have shown that selenoprotein T overexpression inhibits LPS-induced EC apoptosis.[92] It can also directly promote EC regeneration and protect organ function. Lung injury in mice with senile sepsis is associated with impaired endothelial regeneration. FoxM1, a key transcription factor related to cellular repair, has been shown to play an important role in endothelial regeneration in young mice. The use of endothelium-targeting nanoparticles to deliver the *FOXM1* gene *in vivo* can reactivate endothelial regeneration and vascular repair, reduce inflammation, and improve survival in elderly mice following recovery from sepsis.[93]

Strategies for treating sepsis based on ECs may require personalization, organ-specific approaches, and consideration

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of local differences between organs. Sepsis is diagnosed based on clinical signs rather than characteristic signs or symptoms, and encompasses a heterogeneous group of diseases. Molecular and functional differences exist in ECs from different organs or different microvascular segments of the same organ, leading to heterogeneity in their responses to sepsis. Extrapolating the observational results of sepsis based on ECs from one organ or microvascular segment to another is challenging.[94] Although promising results have been observed for preclinical therapies targeting sepsis-induced endothelial dysfunction [Table 2], no such treatments have yet been found to improve survival rates in large-scale randomized clinical trials.[5] The mechanisms underlying sepsis-induced endothelial dysfunction are complex and intertwined. Further in-depth research is therefore required before patients can benefit from EC therapy to effectively treat sepsis.

Limitations

Despite our insights into the roles of ECs in sepsis, this review was subject to several key limitations worth noting. The heterogeneity of ECs may lead to differences in their responses to sepsis in different organs; however, there is currently a lack of targeted studies exploring this variability in the literature. Therefore, further research into this topic is warranted. In addition, although this review summarizes current progress regarding therapeutic interventions targeting endothelial responses, the clinical application of these interventions still faces certain challenges (such as side effects, safety, and efficacy) which should be further investigated and addressed. Future studies should focus on these aspects in order to provide a more reliable basis for clinical treatments.

Conclusion

By comprehensively analyzing the responses of different ECs in patients with sepsis, as well as their varying impacts on organ function, researchers have gained insight into the critical role that ECs play in the pathogenesis of this disease. Not only do ECs play crucial roles in terms of maintaining vascular permeability and regulating inflammation and thrombosis, they are also actively involved in inhibiting bacterial dissemination, coordinating leukocyte recruitment, and clearing bacteria. They accomplish this through the release of cytokines, chemokines, and procoagulant factors, as well as the expression of adhesion molecules. However, prolonged or excessive endothelial activation may lead to impaired microcirculation, inadequate tissue perfusion, and organ dysfunction. These can further exacerbate the severity of sepsis and lead to mortality. Given the heterogeneity of ECs in different organs, differences in endothelial responses may result in different risks of organ damage, thereby providing additional challenges and opportunities for therapeutic interventions that target endothelial responses. The conclusions of this review emphasize the importance of focusing on the endothelial response and suggest the importance of targeted therapeutic interventions. Future studies should focus more on the specific responses of ECs in different organs and the development of targeted therapeutic strategies, with the aim of providing more effective approaches and strategies for the treatment of patients with sepsis.

Table 2: Therapies for sepsis that target ECs.

Targets	Therapies	References
Inhibit inflammation	MicroRNA-145	[24]
	Methylthiouracil	[88]
Inhibit adhesion	Methylthiouracil	[88]
	MicroRNA-223	[97]
Improve coagulation	MicroRNA-19b-3p	[95]
	DPP-4 inhibitors	[99]
Inhibit apoptosis	rhAPC	[56]
	ERRα	[96]
	Selenoprotein T	[99]

DPP-4 inhibitors: Dipeptidyl peptidase-4 inhibitors; ECs: Endothelial cells; ERRα: Estrogen-related receptor alpha; rhAPC: recombinant human activated protein C.

Funding

This work was supported by National Natural Science Foundation of China (Nos. 82202409 and 82372179), Natural Science Foundation of Hubei Province (No. 2022CFA089), and The Interdisciplinary Innovative Talents Foundation from Renmin Hospital of Wuhan University (No. JCRCFZ-2022-007).

Conflicts of interest

None.

References

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, *et al*. Global, regional, and national sepsis incidence and mortality, 1990-2017: Analysis for the Global Burden of Disease Study. Lancet 2020;395:200–211. doi: 10.1016/S0140-6736(19)32989-7.
2. Wang L, Tang Y, Tang J, Liu X, Zi S, Li S, *et al*. Endothelial cell-derived extracellular vesicles expressing surface VCAM1 promote sepsis-related acute lung injury by targeting and reprogramming monocytes. J Extracell Vesicles 2024;13:e12423. doi: 10.1002/jev2.12423.
3. Park YJ, Heo JB, Choi YJ, Cho S, Lee T, Song GY, *et al*. Antiseptic functions of CGK012 against HMGB1-mediated septic responses. Int J Mol Sci 2024;25:2976. doi: 10.3390/ijms25052976.
4. Dolmatova EV, Wang K, Mandavilli R, Griendling KK. The effects of sepsis on endothelium and clinical implications. Cardiovasc Res 2021;117:60–73. doi: 10.1093/cvr/cvaa070.
5. Joffre J, Hellman J, Ince C, Ait-Oufella H. Endothelial responses in sepsis. Am J Respir Crit Care Med 2020;202:361–370. doi: 10.1164/rccm.201910-1911TR.
6. Villalba N, Baby S, Yuan SY. The endothelial glycocalyx as a double-edged sword in microvascular homeostasis and pathogenesis. Front Cell Dev Biol 2021;9:711003. doi: 10.3389/fcell.2021.711003.
7. Cao RN, Tang L, Xia ZY, Xia R. Endothelial glycocalyx as a potential theriapeutic target in organ injuries. Chin Med J 2019;132:963–975. doi: 10.1097/CM9.0000000000000177.
8. Li N, Hao R, Ren P, Wang J, Dong J, Ye T, *et al*. Glycosaminoglycans: Participants in microvascular coagulation of sepsis. Thromb Haemost 2024;124:599–612. doi: 10.1055/a-2250-3166.
9. Song Z, Wang Z, Cai J, Zhou Y, Jiang Y, Tan J, *et al*. Down-regulating lncRNA KCNQ1OT1 relieves type II alveolar epithelial cell apoptosis during one-lung ventilation via modulating miR-129-5p/

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HMGB1 axis induced pulmonary endothelial glycocalyx. Environ Toxicol 2024;39:3578–3596. doi: 10.1002/tox.24201.
10. Machin DR, Sabouri M, Zheng X, Donato AJ. Therapeutic strategies targeting the endothelial glycocalyx. Curr Opin Clin Nutr Metab Care 2023;26:543–550. doi: 10.1097/MCO.0000000000000973.
11. Urban C, Hayes HV, Piraino G, Wolfe V, Lahni P, O'Connor M, *et al*. Colivelin, a synthetic derivative of humanin, ameliorates endothelial injury and glycocalyx shedding after sepsis in mice. Front Immunol 2022;13:984298. doi: 10.3389/fimmu.2022.984298.
12. Fernández-Sarmiento J, Molina CF, Salazar-Pelaez LM, Flórez S, Alarcón-Forero LC, Sarta M, *et al*. Biomarkers of glycocalyx injury and endothelial activation are associated with clinical outcomes in patients with sepsis: A systematic review and meta-analysis. J Intensive Care Med 2023;38:95–105. doi: 10.1177/08850666221109186.
13. Wei C, Jiang W, Wang R, Zhong H, He H, Gao X, *et al*. Brain endothelial GSDMD activation mediates inflammatory BBB breakdown. Nature 2024;629:893–900. doi: 10.1038/s41586-024-07314-2.
14. Li X, Wang S, Luo M, Wang M, Wu S, Liu C, *et al*. Carnosol alleviates sepsis-induced pulmonary endothelial barrier dysfunction by targeting nuclear factor erythroid2-related factor 2/sirtuin-3 signaling pathway to attenuate oxidative damage. Phytother Res 2024;38:2182–2197. doi: 10.1002/ptr.8138.
15. Zhang H, Zhang X, Ling C, Liu C, Hua S, Xiong Z, *et al*. EGFR-TNFR1 pathway in endothelial cell facilitates acute lung injury by NF-κB/MAPK-mediated inflammation and RIP3-dependent necroptosis. Int Immunopharmacol 2023;117:109902. doi: 10.1016/j.intimp.2023.109902.
16. Zhan F, Zhang J, He P, Chen W, Ouyang Y. Macrophage-derived exosomal miRNA-141 triggers endothelial cell pyroptosis by targeting NLRP3 to accelerate sepsis progression. Int J Immunopathol Pharmacol 2024;38:1210454832. doi: 10.1177/03946320241234736.
17. Haileselassie B, Joshi AU, Minhas PS, Mukherjee R, Andreasson KI, Mochly-Rosen D. Mitochondrial dysfunction mediated through dynamin-related protein 1 (Drp1) propagates impairment in blood brain barrier in septic encephalopathy. J Neuroinflammation 2020;17:36. doi: 10.1186/s12974-019-1689-8.
18. Joffre J, Hellman J. Oxidative stress and endothelial dysfunction in sepsis and acute inflammation. Antioxid Redox Signal 2021;35:1291–1307. doi: 10.1089/ars.2021.0027.
19. Bai R, Pei J, Pei S, Cong X, Chun J, Wang F, *et al*. LPA_2 alleviates septic acute lung injury via protective endothelial barrier function through activation of PLC-PKC-FAK. J Inflamm Res 2023;16:5095–5109. doi: 10.2147/JIR.S419578.
20. Qian T, Qi B, Fei Y, Li J, Luo L, Lv B, *et al*. PLD2 deletion alleviates disruption of tight junctions in sepsis-induced ALI by regulating PA/STAT3 phosphorylation pathway. Int Immunopharmacol 2023;114:109561. doi: 10.1016/j.intimp.2022.109561.
21. Xing Y, Cheng D, Shi C. Protective effect of shenfu injection on the endothelium of severe sepsis by inhibiting $CD11b^+$cell paralysis induced by high mobility group protein B1 (in Chinese). Chin Crit Care Med 2020;32:696–701. doi: 10.3760/cma.j.cn121430-20191127-00066.
22. He J, Jing D, Zhao S, Duan M. BAP31 promotes adhesion between endothelial cells and macrophages through the NF-κB signaling pathway in sepsis. J Inflamm Res 2024;17:1267–1279. doi: 10.2147/JIR.S448091.
23. Hu Z, Dai J, Xu T, Chen H, Shen G, Zhou J, *et al*. FGF18 alleviates sepsis-induced acute lung injury by inhibiting the NF-κB pathway. Respir Res 2024;25:108. doi: 10.1186/s12931-024-02733-1.
24. Lin Y, Liu L, Lin Y, Yang R, Liao S, Xu M, *et al*. MiR-145 alleviates sepsis-induced inflammatory responses and organ injury by targeting ADAM17. Front Biosci (Landmark Ed) 2024;29:44. doi: 10.31083/j.fbl2901044.
25. Miao J, Li L, Shaheen N, Wei J, Jacko AM, Sundd P, *et al*. The deubiquitinase USP40 preserves endothelial integrity by targeting the heat shock protein HSP90β. Exp Mol Med 2024;56:395–407. doi: 10.1038/s12276-024-01160-y.
26. Carman CV, Nikova DN, Sakurai Y, Shi J, Novakovic VA, Rasmussen JT, *et al*. Membrane curvature and PS localize coagulation proteins to filopodia and retraction fibers of endothelial cells. Blood Adv 2023;7:60–72. doi: 10.1182/bloodadvances.2021006870.
27. Tschirhart BJ, Lu X, Gomes J, Chandrabalan A, Bell G, Hess DA, *et al*. Annexin A5 inhibits endothelial inflammation induced by lipopolysaccharide-activated platelets and microvesicles via phosphatidylserine binding. Pharmaceuticals (Basel) 2023;16:837. doi: 10.3390/ph16060837.
28. Fritsche L, Löffler D, Kantartzis K, Flehmig G, Roden M, Fritsche A, *et al*. Impact of breastfeeding duration on coagulation in women with and without history of gestational diabetes mellitus. J Clin Endocrinol Metab 2024:dgae172. doi: 10.1210/clinem/dgae172.
29. Tanaka K, Harada H, Kamuro H, Sakai H, Yamamoto A, Tomimatsu M, *et al*. Arid5a/IL-6/PAI-1 signaling is involved in the pathogenesis of lipopolysaccharide-induced kidney injury. Biol Pharm Bull 2023;46:1753–1760. doi: 10.1248/bpb.b23-00482.
30. Bruno MEC, Mukherjee S, Stromberg AJ, Saito H, Starr ME. Visceral fat-specific regulation of plasminogen activator inhibitor-1 in aged septic mice. J Cell Physiol 2022;237:706–719. doi: 10.1002/jcp.30551.
31. Guo J, Xu QH. The correlation of plasma thrombomodulin plasminogen activator inhibitor-1 and endothelial cell injury in septic patients (in Chinese). Chin J Intern Med 2021;60:143–146. doi: 10.3760/cma.j.cn112138-20200330-00319.
32. Kaminski TW, Brzoska T, Li X, Vats R, Katoch O, Dubey RK, *et al*. Lung microvascular occlusion by platelet-rich neutrophil-platelet aggregates promotes cigarette smoke-induced severe flu. JCI Insight 2024;9:e167299. doi: 10.1172/jci.insight.167299.
33. Macdonald S, Bosio E, Shapiro NI, Balmer L, Burrows S, Hibbs M, *et al*. No association between intravenous fluid volume and endothelial glycocalyx shedding in patients undergoing resuscitation for sepsis in the emergency department. Sci Rep 2022;12:8733. doi: 10.1038/s41598-022-12752-x.
34. Choroszy M, Środa-Pomianek K, Wawrzyńska M, Chmielarz M, Bożemska E, Sobieszczańska B. The role of palmitic acid in the co-toxicity of bacterial metabolites to endothelial cells. Vasc Health Risk Manag 2023;19:399–409. doi: 10.2147/VHRM.S408897.
35. Yu H, Liu Q, Chen G, Huang L, Luo M, Lv D, *et al*. SIRT3-AMPK signaling pathway as a protective target in endothelial dysfunction of early sepsis. Vasc Health Risk Manag 2022;106:108600. doi: 10.1016/j.intimp.2022.108600.
36. Hu S, Pi Q, Luo M, Cheng Z, Liang X, Luo S, *et al*. Contribution of the NLRP3/IL-1β axis to impaired vasodilation in sepsis through facilitation of eNOS proteolysis and the protective role of melatonin. Int Immunopharmacol 2021;93:107388. doi: 10.1016/j.intimp.2021.107388.
37. Siegel PM, Bojti I, Bassler N, Holien J, Flierl U, Wang X, *et al*. A DARPin targeting activated Mac-1 is a novel diagnostic tool and potential anti-inflammatory agent in myocarditis, sepsis and myocardial infarction. Basic Res Cardiol 2021;116:17. doi: 10.1007/s00395-021-00849-9.
38. Cleuren A, Molema G. Organotypic heterogeneity in microvascular endothelial cell responses in sepsis-a molecular treasure trove and pharmacological Gordian knot. Front Med (Lausanne) 2023;10:1252021. doi: 10.3389/fmed.2023.1252021.
39. Betsholtz C. Toward a granular molecular-anatomic map of the blood vasculature–single-cell RNA sequencing makes the leap. Ups J Med Sci 2022;127. doi: 10.48101/ujms.v127.9051.
40. Maneta E, Aivalioti E, Tual-Chalot S, Emini Veseli B, Gatsiou A, Stamatelopoulos K, *et al*. Endothelial dysfunction and immunothrombosis in sepsis. Front Immunol 2023;14:1144229. doi: 10.3389/fimmu.2023.1144229.
41. Zwiers PJ, Lucas JPFE, Jongman RM, van Meurs M, Popa ER, Molema G. Reduced Tie2 in microvascular endothelial cells is associated with organ-specific adhesion molecule expression in murine health and endotoxemia. Cells 2023;12:1850. doi: 10.3390/cells12141850.
42. Amersfoort J, Eelen G, Carmeliet P. Immunomodulation by endothelial cells – partnering up with the immune system? Nat Rev Immunol 2022;22:576–588. doi: 10.1038/s41577-022-00694-4.
43. Krausgruber T, Fortelny N, Fife-Gernedl V, Senekowitsch M, Schuster LC, Lercher A, *et al*. Structural cells are key regulators of organ-specific immune responses. Nature 2020;583:296–302. doi: 10.1038/s41586-020-2424-4.
44. Colás-Algora N, Muñoz-Pinillos P, Cacho-Navas C, Avendaño-Ortiz J, de Rivas G, Barroso S, *et al*. Simultaneous targeting of IL-1-signaling and IL-6-trans-signaling preserves human pulmonary endothelial barrier function during a cytokine storm-brief report. Arterioscler Thromb Vasc Biol 2023;43:2213–2222. doi: 10.1161/ATVBAHA.123.319695.
45. Zhu S, Yu Y, Qu M, Qiu Z, Zhang H, Miao C, *et al*. Neutrophil extracellular traps contribute to immunothrombosis formation via the STING pathway in sepsis-associated lung injury. Cell Death Discov 2023;9:315. doi: 10.1038/s41420-023-01614-8.

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46. Mahamed Z, Shadab M, Najar RA, Millar MW, Bal J, Pressley T, *et al*. The protective role of mitochondria-associated endoplasmic reticulum membrane (MAM) protein sigma-1 receptor in regulating endothelial inflammation and permeability associated with acute lung injury. Cells 2023;13:5. doi: 10.3390/cells13010005.
47. Price DR, Garcia JGN. A razor's edge: Vascular responses to acute inflammatory lung injury/acute respiratory distress syndrome. Annu Rev Physiol 2024;86:505–529. doi: 10.1146/annurev-physiol-042222-030731.
48. Yang R, Zheng T, Xiang H, Liu M, Hu K. Lung single-cell RNA profiling reveals response of pulmonary capillary to sepsis-induced acute lung injury. Front Immunol 2024;15:1308915. doi: 10.3389/fimmu.2024.1308915.
49. Mu ST, Tang J, Ma JQ, Zhong Y, Liu HZ, Ma XC, *et al*. Unfractionated heparin attenuates endothelial barrier dysfunction via the phosphatidylinositol-3 kinase/serine/threonine kinase/nuclear factor kappa-B pathway. Chin Med J 2020;133:1815–1823. doi: 10.1097/CM9.0000000000000905.
50. Dolmatova EV, Forrester SJ, Wang K, Ou Z, Williams HC, Joseph G, *et al*. Endothelial Poldip2 regulates sepsis-induced lung injury via Rho pathway activation. Cardiovasc Res 2022;118:2506–2518. doi: 10.1093/cvr/cvab295.
51. Atreya MR, Cvijanovich NZ, Fitzgerald JC, Weiss SL, Bigham MT, Jain PN, *et al*. Prognostic and predictive value of endothelial dysfunction biomarkers in sepsis-associated acute kidney injury: Risk-stratified analysis from a prospective observational cohort of pediatric septic shock. Crit Care 2023;27:260. doi: 10.1186/s13054-023-04554-y.
52. Betrie AH, Ma S, Ow CPC, Peiris RM, Evans RG, Ayton S, *et al*. Renal arterial infusion of tempol prevents medullary hypoperfusion, hypoxia, and acute kidney injury in ovine Gram-negative sepsis. Acta Physiol (Oxf) 2023;239:e14025. doi: 10.1111/apha.14025.
53. Iba T, Helms J, Maier CL, Levi M, Scarlatescu E, Levy JH. The role of thromboinflammation in acute kidney injury among patients with septic coagulopathy. J Thromb Haemost 2024;22:1530–1540. doi: 10.1016/j.jtha.2024.02.006.
54. Pode-Shakked N, Ceschia G, Rose JE, Goldstein SL, Stanski NL; Genomics of Pediatric Septic Shock Investigators. Increasing angiotensin-converting enzyme concentrations and absent angiotensin-converting enzyme activity are associated with adverse kidney outcomes in pediatric septic shock. Crit Care 2023;27:230. doi: 10.1186/s13054-023-04518-2.
55. Yu WK, McNeil JB, Wickersham NE, Shaver CM, Bastarache JA, Ware LB. Vascular endothelial cadherin shedding is more severe in sepsis patients with severe acute kidney injury. Crit Care 2019;23:18. doi: 10.1186/s13054-019-2315-y.
56. Gatica S, Villegas V, Vallejos A, Olivares P, Aballai V, Lagos-Meza F, *et al*. TRPM7 mediates kidney injury, endothelial hyperpermeability and mortality during endotoxemia. Lab Invest 2020;100:234–249. doi: 10.1038/s41374-019-0304-z.
57. Wang X, Wang Y, Huo H, Zhou G, Li Y, Liang F, *et al*. Transient receptor vanilloid subtype 4-mediated Ca^{2+} influx promotes glomerular endothelial inflammation in sepsis-associated acute kidney injury. Lab Invest 2023;103:100126. doi: 10.1016/j.labinv.2023.100126.
58. Sonneville R, Benghanem S, Jeantin L, de Montmollin E, Doman M, Gaudemer A, *et al*. The spectrum of sepsis-associated encephalopathy: A clinical perspective. Crit Care 2023;27:386. doi: 10.1186/s13054-023-04655-8.
59. Mazeraud A, Righy C, Bouchereau E, Benghanem S, Bozza FA, Sharshar T. Septic-associated encephalopathy: A comprehensive review. Neurotherapeutics 2020;17:392–403. doi: 10.1007/s13311-020-00862-1.
60. Tauber SC, Djukic M, Gossner J, Eiffert H, Brück W, Nau R. Sepsis-associated encephalopathy and septic encephalitis: An update. Expert Rev Anti Infect Ther 2021;19:215–231. doi: 10.1080/14787210.2020.1812384.
61. Barichello T, Giridharan VV, Catalão CHR, Ritter C, Dal-Pizzol F. Neurochemical effects of sepsis on the brain. Clin Sci (Lond) 2023;137:401–414. doi: 10.1042/CS20220549.
62. Denes A, Hansen CE, Oezorhan U, Figuerola S, de Vries HE, Sorokin L, *et al*. Endothelial cells and macrophages as allies in the healthy and diseased brain. Acta Neuropathol 2024;147:38. doi: 10.1007/s00401-024-02695-0.
63. Villalba N, Baby S, Cha BJ, Yuan SY. Site-specific opening of the blood-brain barrier by extracellular histones. J Neuroinflammation 2020;17:281. doi: 10.1186/s12974-020-01950-x.
64. Erikson K, Tuominen H, Vakkala M, Liisanantti JH, Karttunen T, Syrjälä H, *et al*. Brain tight junction protein expression in sepsis in an autopsy series. Crit Care 2020;24:385. doi: 10.1186/s13054-020-03101-3.
65. Huang WY, Lai YL, Liu KH, Lin S, Chen HY, Liang CH, *et al*. TNFα-mediated necroptosis in brain endothelial cells as a potential mechanism of increased seizure susceptibility in mice following systemic inflammation. J Neuroinflammation 2022;19:29. doi: 10.1186/s12974-022-02406-0.
66. Yue J, Tan Y, Huan R, Guo J, Yang S, Deng M, *et al*. Mast cell activation mediates blood-brain barrier impairment and cognitive dysfunction in septic mice in a histamine-dependent pathway. Front Immunol 2023;14:1090288. doi: 10.3389/fimmu.2023.1090288.
67. Kodali MC, Chen H, Liao FF. Temporal unsnarling of brain's acute neuroinflammatory transcriptional profiles reveals panendothelitis as the earliest event preceding microgliosis. Mol Psychiatry 2021;26:3905–3919. doi: 10.1038/s41380-020-00955-5.
68. Wang P, Wang W, Hu Y, Li Y. Prolonged soluble epoxide hydrolase reactivity in brain endothelial cells is associated with long cognitive deficits in sepsis. Mol Neurobiol 2020;57:2846–2855. doi: 10.1007/s12035-020-01925-2.
69. Asby D, Boche D, Allan S, Love S, Miners JS. Systemic infection exacerbates cerebrovascular dysfunction in Alzheimer's disease. Brain 2021;144:1869–1883. doi: 10.1093/brain/awab094.
70. Elkind MSV, Boehme AK, Smith CJ, Meisel A, Buckwalter MS. Infection as a stroke risk factor and determinant of outcome after stroke. Stroke 2020;51:3156–3168. doi: 10.1161/STROKEAHA.120.030429.
71. Hollenberg SM, Singer M. Pathophysiology of sepsis-induced cardiomyopathy. Nat Rev Cardiol 2021;18:424–434. doi: 10.1038/s41569-020-00492-2.
72. Frencken JF, van Smeden M, van de Groep K, Ong DSY, Klein Klouwenberg PMC, Juffermans N, *et al*. Etiology of myocardial injury in critically ill patients with sepsis: A cohort study. Ann Am Thorac Soc 2022;19:773–780. doi: 10.1513/AnnalsATS.202106-689OC.
73. Rossouw TM, Anderson R, Manga P, Feldman C. Emerging role of platelet-endothelium interactions in the pathogenesis of severe SARS-CoV-2 infection-associated myocardial injury. Front Immunol 2022;13:776861. doi: 10.3389/fimmu.2022.776861.
74. Zhang X, Wang X, Fan M, Tu F, Yang K, Ha T, *et al*. Endothelial HSPA12B exerts protection against sepsis-induced severe cardiomyopathy via suppression of adhesion molecule expression by miR-126. Front Immunol 2020;11:566. doi: 10.3389/fimmu.2020.00566.
75. Üstündağ H, Doğanay S, Kalındemirtaş FD, Demir Ö, Huyut MT, Kurt N, *et al*. A new treatment approach: Melatonin and ascorbic acid synergy shields against sepsis-induced heart and kidney damage in male rats. Life Sci 2023;329:121875. doi: 10.1016/j.lfs.2023.121875.
76. Zou R, Shi W, Chang X, Zhang M, Tan S, Li R, *et al*. The DNA-dependent protein kinase catalytic subunit exacerbates endotoxemia-induced myocardial microvascular injury by disrupting the MOTS-c/JNK pathway and inducing profilin-mediated lamellipodia degradation. Theranostics 2024;14:1561–1582. doi: 10.7150/thno.92650.
77. Xie Z, Shao B, Hoover C, McDaniel M, Song J, Jiang M, *et al*. Monocyte upregulation of podoplanin during early sepsis induces complement inhibitor release to protect liver function. JCI Insight 2020;5:e134749. doi: 10.1172/jci.insight.134749.
78. Jiang J, Liu D, Wang Y, Li W, Hong Z, An J, *et al*. Glaucocalyxin a protect liver function via inhibiting platelet over-activation during sepsis. Phytomedicine 2022;100:154089. doi: 10.1016/j.phymed.2022.154089.
79. Chen G, Ren C, Xiao Y, Wang Y, Yao R, Wang Q, *et al*. Time-resolved single-cell transcriptomics reveals the landscape and dynamics of hepatic cells in sepsis-induced acute liver dysfunction. JHEP Rep 2023;5:100718. doi: 10.1016/j.jhepr.2023.100718.
80. Gracia-Sancho J, Caparrós E, Fernández-Iglesias A, Francés R. Role of liver sinusoidal endothelial cells in liver diseases. Nat Rev Gastroenterol Hepatol 2021;18:411–431. doi: 10.1038/s41575-020-00411-3.
81. He XL, Chen JY, Feng YL, Song P, Wong YK, Xie LL, *et al*. Single-cell RNA sequencing deciphers the mechanism of sepsis-induced liver injury and the therapeutic effects of artesunate. Acta Pharmacol Sin 2023;44:1801–1814. doi: 10.1038/s41401-023-01065-y.
82. Sun X, Wu J, Liu L, Chen Y, Tang Y, Liu S, *et al*. Transcriptional switch of hepatocytes initiates macrophage recruitment and T-cell

suppression in endotoxemia. J Hepatol 2022;77:436–452. doi: 10.1016/j.jhep.2022.02.028.
83. Iba T, Helms J, Connors JM, Levy JH. The pathophysiology, diagnosis, and management of sepsis-associated disseminated intravascular coagulation. J Intensive Care 2023;11:24. doi: 10.1186/s40560-023-00672-5.
84. Iba T, Connors JM, Nagaoka I, Levy JH. Recent advances in the research and management of sepsis-associated DIC. Int J Hematol 2021;113:24–33. doi: 10.1007/s12185-020-03053-y.
85. Jiménez-Dinamarca I, Prado Y, Tapia P, Gatica S, Alt C, Lin CP, *et al*. Disseminated intravascular coagulation phenotype is regulated by the TRPM7 channel during sepsis. Biol Res 2023;56:8. doi: 10.1186/s40659-023-00419-4.
86. Luo L, Xu M, Liao D, Deng J, Mei H, Hu Y. PECAM-1 protects against DIC by dampening inflammatory responses via inhibiting macrophage pyroptosis and restoring vascular barrier integrity. Transl Res 2020;222:1–16. doi: 10.1016/j.trsl.2020.04.005.
87. Bao W, Xing H, Cao S, Long X, Liu H, Ma J, *et al*. Neutrophils restrain sepsis associated coagulopathy via extracellular vesicles carrying superoxide dismutase 2 in a murine model of lipopolysaccharide induced sepsis. Nat Commun 2022;13:4583. doi: 10.1038/s41467-022-32325-w.
88. Kwak S, Ku SK, Kang H, Baek MC, Bae JS. Methylthiouracil, a new treatment option for sepsis. Vascul Pharmacol 2017;88:1–10. doi: 10.1016/j.vph.2015.07.013.
89. Hauschildt J, Schrimpf C, Thamm K, Retzlaff J, Idowu TO, von Kaisenberg C, *et al*. Dual pharmacological inhibition of angiopoietin-2 and VEGF-A in murine experimental sepsis. J Vasc Res 2020;57:34–45. doi: 10.1159/000503787.
90. Zhang Y, Li J, Jing Q, Chen Z, Wang K, Sun C. An erythrocyte membrane-derived nanosystem for efficient reversal of endothelial injury in sepsis. Adv Healthc Mater 2024;13:e2302320. doi: 10.1002/adhm.202302320.
91. Hakanpaa L, Kiss EA, Jacquemet G, Miinalainen I, Lerche M, Guzmán C, *et al*. Targeting beta1-integrin inhibits vascular leakage in endotoxemia. Proc Natl Acad Sci U S A 2018;115:E6467–E6476. doi: 10.1073/pnas.1722317115.
92. Zhang R, Lu S, Yang X, Li M, Jia H, Liao J, *et al*. miR-19a-3p downregulates tissue factor and functions as a potential therapeutic target for sepsis-induced disseminated intravascular coagulation. Biochem Pharmacol 2021;192:114671. doi: 10.1016/j.bcp.2021.114671.
93. Huang X, Zhang X, Machireddy N, Evans CE, Trewartha SD, Hu G, *et al*. Endothelial FoxM1 reactivates aging-impaired endothelial regeneration for vascular repair and resolution of inflammatory lung injury. Sci Transl Med 2023;15:eabm5755. doi: 10.1126/scitranslmed.abm5755.
94. Molema G, Zijlstra JG, van Meurs M, Kamps JAAM. Renal microvascular endothelial cell responses in sepsis-induced acute kidney injury. Nat Rev Nephrol 2022;18:95–112. doi: 10.1038/s41581-021-00489-1.
95. Jiang L, Wang M, Sun R, Lin Z, Liu R, Cai H, *et al*. Methylation of miR-19b-3p promoter exacerbates inflammatory responses in sepsis-induced ALI via targeting KLF7. Cell Biol Int 2021;45:1666–1675. doi: 10.1002/cbin.11601.
96. Xia W, Pan Z, Zhang H, Zhou Q, Liu Y. ERRα protects against sepsis-induced acute lung injury in rats. Mol Med 2023;29:76. doi: 10.1186/s10020-023-00670-1.
97. Szilágyi B, Fejes Z, Rusznyák Á, Fenyvesi F, Pócsi M, Halmi S, *et al*. Platelet microparticles enriched in miR-223 reduce ICAM-1-dependent vascular inflammation in septic conditions. Front Physiol 2021;12:658524. doi: 10.3389/fphys.2021.658524.
98. Wang SC, Wang XY, Liu CT, Chou RH, Chen ZB, Huang PH, *et al*. The dipeptidyl peptidase-4 inhibitor linagliptin ameliorates endothelial inflammation and microvascular thrombosis in a sepsis mouse model. Int J Mol Sci 2022;23:3065. doi: 10.3390/ijms23063065.
99. Merk D, Ptok J, Jakobs P, von Ameln F, Greulich J, Kluge P, *et al*. Selenoprotein T protects endothelial cells against lipopolysaccharide-induced activation and apoptosis. Antioxidants (Basel) 2021;10:1427. doi: 10.3390/antiox10091427.

How to cite this article: Wu M, Yan Y, Xie XY, Bai JW, Ma CT, Du XJ. Effect of endothelial responses on sepsis-associated organ dysfunction. Chin Med J 2024;XXX:1–11. doi: 10.1097/CM9.0000000000003342

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